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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/438,944	11/12/99	STEWART M	T57005US

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EXAMINER	
DECLOUX, A	
ART UNIT	PAPER NUMBER
1644	11

DATE MAILED: 05/04/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/438,944	Stewart, M. et al.
Examiner	**Art Unit**
DeCloux, Amy	1644

-- The MAILING DATE of this communication appears on th cov r sh t with th correspond nc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *faxed 2-14-01*

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *12-21* is/are pending in the applica

4a) Of the above, claim(s) _____ is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *12-21* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 2, 9

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☒ Other: Notice to Comply with Requirements For Sequence Disclosures

DETAILED ACTION

1. Applicant's election of Group II, claims 12-21 in Paper No. 10, faxed 2-14-01 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse MPEP8.03(a)).

Applicant's election in Paper No. 10, faxed 2-14-01, of the species "an antibody" from the list of targeting agents listed in claim 14, and the species "von Willebrand factor" from the list of platelet specific components listed in claim 17, is also acknowledged.

2. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

3. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Sequences are disclosed in the specification, specifically on page 36, Table 2. Applicants are required to submit a disk and paper copy of the sequences according to the attached "Notice to Comply with the Sequence Rules." In addition to the paper copy required by paragraph © of this section and the computer readable form required by paragraph (e) of this section, a statement that the content of the paper and computer readable copies are the same must be submitted with the computer readable form. Such a statement must be a verified statement if made by a person not registered to practice before the Office. Applicant is reminded of the sequence rules which require a submission for all sequences of more than 9 nucleotides or 3 amino acids (see 37 C.F.R. 1.821-1.825) and is also requested to carefully review the submitted specification for any and all sequences which require compliance with the rules.

4. Applicant should amend the first line of the specification to update the status (and relationship) of the priority documents. The first sentence of the specification should refer to the provisional application using language such as:
This application claims the benefit of U.S. Provisional Application No. 60/108,129, filed

11/12/1998. See MPEP 1302.04.

5. Acknowledgment is made of applicant's claim for priority under 35 U.S.C. 119(a)-(d) based upon an application filed in IB? on 11/10/1999. A claim for priority under 35 U.S.C. 119(a)-(d) cannot be based on said application, since the United States application was filed more than twelve months thereafter.

6. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: Claim 18 lacks an antecedent basis for the phrase "homophyllic peptides". It is suggested that the Applicants amend the specification to include this limitation, in order to overcome this rejection.

7. *35 U.S.C. § 101* reads as follows:

"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

8. Claim 12 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).The instant claim, which recites a method of inducing thrombus in vivo, does not recite the administration of anything and thus encompasses the natural process of thrombus formation in vivo.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 17 and 21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

In the instant case, the specification does not convey to the artisan that the applicant had possession, at the time of invention, of the claimed peptide mimetic of VEGF or VEGF-like molecule bond to the VEGF receptor,

as recited in claim 21. Furthermore, the specification does not convey to the artisan that the applicant had possession, at the time of invention, of the functional equivalent of any of the platelet-specific components recited in claim 17.

Due to this broad definitions of these recitations, none of these recitations meets the written description provision of 35 USC 112, first paragraph. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See Vas-Cath, page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath, page 1116.).

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.) Applicants are directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday December 21, 1999.

11. Claims 12-17 and 19-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for inducing thrombus in vivo comprising a bifunctional targeting component which binds to a VEGF/VEGF receptor, does not reasonably provide enablement for said method comprising targeting component that binds any ligand/receptor complex, or any growth factor/growth factor receptor or any peptide mimetic or any VEGF-like molecule bound to the VEGF receptor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The disclosure of the instant specification is insufficient to enable one skilled in the art to practice the invention as broadly claimed in claims 19-21 without an undue amount of experimentation. Besides a method for inducing thrombus in vitro comprising a targeting component which binds to a VEGF/VEGF receptor, the instant specification provides insufficient guidance for the efficacy of said method comprising any ligand/receptor complex, or any growth factor/growth factor receptor, or any peptide mimetic of VEGF or any VEGF-like molecule bound to the VEGF receptor. For instance, a method for inducing thrombus in vivo comprising a targeting component that binds to a ligand/receptor complex that is located exclusively in the nucleus of a cell would not be an effective since the thrombus formation does not occur

intra cellularly. Similarly, a method for inducing thrombus in vivo comprising a growth factor/growth factor receptor that is not present in a location containing platelets, would not be an effective for thrombus formation due to lack of contact with platelets. Furthermore, the instant specific fails to provide sufficient guidance to make and use in the claimed method any peptide mimetic of VGEF or VGF-like molecule bound to the VEGF receptor, and therefore it would require undue experimentation to predict which peptide mimetic of VGEF or VGF-like molecule bound to the VEGF receptor would be effective in thrombus formation in the method as claimed.

Furthermore, the instant specific fails to provide sufficient guidance to make and use in the claimed method a bifunctional targeting agent that comprises a platelet-specific component which comprises a functional equivalent of Willebrand factor or of any other components as recited in claim 17, and therefore it would require undue experimentation to predict which functional equivalent would be effective in thrombus formation in the method as claimed.

Furthermore, claim 12 is an incomplete claim because there is no recitation of an active step by the practitioner of the method--IE nothing is administered to induce thrombus in vivo as recited in the preamble of claim 12.

In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, it would take undue trials and errors to practice the claimed invention.

12. The following is a quotation of the second paragraph of 35 U.S.C.112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his invention.

13. Claims 12-21 are rejected under *35 U.S.C. § 112*, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

A) Claim 16 and dependent claims 17-21 are indefinite in their recitation of the phrase "a platelet-specific component" in claim 16 because it is not clear if said phrase comprises a component integral to platelets or if said phrase comprises a component that specifically binds to platelets. The latter interpretation is being used for examination purposes because dependent claim 17 recites a group of platelet specific components which are not intrinsic to platelets.

B) Claim 21 is indefinite in the recitation of the phrase "receptor is VEGF/VEGF receptor or a peptide mimetic of VEGF or VEGF-like molecule bound to the VEGF receptor because said phrase can be interpreted two ways. One interpretation is that the peptide mimetic is a peptide mimetic of either VEGF or a VEGF-like molecule, and

that said mimetic is bound to the VGF receptor. Another interpretation is that the peptide mimetic is of VEGF only and that only the VEGF-like molecule is bound to the VEGF receptor. The former interpretation is being used for examination purposes.

C) Claims 12-21 are indefinite in the recitation of the phrase "inducing thrombus in vivo" (see line 1 of claim 12) because the meaning is unclear. Perhaps an "a" could be inserted before "thrombus", or "formation" could be inserted after "thrombus".

D) Claims 13-21 are indefinite in the recitation of "inducing platelets to collect at a predetermined site " (see claim 13, lines 1-2) because of the lack of antecedent basis. (Claim 12, from which claim 13 depends, recites "capturing platelets at a selected site" and "inducing activation of the platelets")

E) Claim 12 is indefinite because there is no active step conducted by the practitioner of the method: i.e. nothing is administered to initiate the process.

14. The following is a quotation of the appropriate paragraphs of *35 U.S.C. § 102* that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

15. Claims 12-17 and 19-21 are rejected under 35 U.S.C. 102(b)/(e) as being anticipated by Thorpe et al. (WO 96/01653) and (US Patent # 6,093,399).

In WO 96/01653, Thorpe et al teach a method of inducing thrombus in vivo comprising capturing platelets at a selected site (tumor vasculature (endothelial cells)) by administering a targeting agent (a bispecific antibody, see pages 17-18, 24), one component of which specifically binds a disease associated vasculature marker (specifically the VEGF/VEGF receptor (pages 12 and 17)), inducing activation of the platelets and inducing a thrombus to form, as recited in claims 12-16 and 19-21. Thorpe et al also teach that the molecules to be targeted using the bispecific ligands or antibodies in said method are those that are expressed on tumor vasculature at a higher level than on normal endothelial cells (see page 61, lines 17-21) and include antibodies to vascular endothelial cell markers that are known to be present on the tumor vascular endothelial cells including those directed to vWF (see page 61, lines 17-35 and Table IV and column 78, lines 6-21), as recited in claims 12-17. Therefore, the referenced teachings anticipate the claimed invention.

In US Patent # 6,093,399, Thorpe et al teach a method of inducing thrombus in vivo comprising capturing platelets at a selected site by administering a targeting agent

(a bispecific antibody column 8) one component of which specifically platelet-specific components including fibrin and heparin (see column 8, lines 39-46) as recited in claims 12-17. Thorpe et al also teach and that a component of a bispecific antibody in said method can bind cella ligand that binds to a tumor vasculature cell surface receptor including a growth factor/growth factor receptor VEGF/VPF, FGF and TGFbeta (see column 7, lines -24) as recited in claims 19-21.Thorpe et al also teach that the molecules to be targeted using the bispecific ligands or antibodies are those that are expressed on tumor vasculature at a higher level than on normal endothelial cells (see column 30, lines 41-44) and include antibodies to vascular endothelial cell markers that are known to be present on the tumor vascular endothelial cells including those directed to vWF (see Table IV and column 38, lines 40-50), as recited in claims 12-17.

16. Claims 12-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Xianming Huang et al. (Science 275:482-484)(January, 1997).

Xianming Huang et al teach a method of inducing thrombus in vivo comprising capturing platelets at a selected site (tumor vasculature(endothelial cells)) by administering a targeting agent (a bispecific antibody) that specifically binds platelets (an experimentally induced marker(MHC Class II)) ; inducing activation of the platelets (by means of the a truncated form of tissue factor when attached to said antibody) and allowing a thrombus to form. Therefore, the referenced teachings anticipate the claimed invention.

17. Claim 12 is rejected under 35 U.S.C. 102(b) as being anticipated by Xianming Huang et al (Science 275:547-550)(January 1997).

Huang et al teach that human tissue factor (TF) is the major initiating receptor for the thrombogenic cascade, and that TF complexes with TF:VI/VIIa to form a complex which leads to the formation of thrombin and ultimately a blood clot (thrombus), (see entire article, especially page 547, column 1, second paragraph). In view of the lack of an active step encompassing the administration of something, the instant claim reads on the natural thrombus formation process. Therefore, the referenced teachings anticipate the claimed invention.

18. The following is a quotation of *35 U.S.C. § 103* which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under *subsection (f)*

or (g) of *section 102* of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

19. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

20. Claims 12-16 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thorpe et al. (US Patent # 6,093,399) in view of Anthony-Cahil et al (U.S. Patent 6218,513).

Thorpe et al teach a method as described above and also teach said method wherein the bifunctional targeting agent described as a bispecific ligand -coagulation factor may be linked by avidin-biotin combinations (see column 9, lines 39-51) as recited by claims 18. But Thorpe et al does not teach said method wherein said a bifunctional binding agent comprises a biotin mimetic as recited in claim 18.

'513 teaches biotin mimetic peptides ("BMP") have been described, and that. Globin fused to a BMP interacts specifically with tetrameric avidin or streptavidin to form a tetrameric globin(see entire patent, especially column 9, lines 61-67 and column 10, lines 1-4)

Therefore, it would have been obvious to one of skill in the art who wanted to induce a thrombus in the tumor vasculature for treatment of a tumor to substitute a biotin mimetic as taught by '513 for biotin in a bifunctional binding agent in said method taught by Thorpe et al since '513 teaches that the biotin mimetic binds avidin and streptavidin as does biotin, and so would be the functional equivalent of biotin in terms of linking subunits together in said method. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

21. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the

examiner should be directed to Amy DeCloux whose telephone number is (703) 306-5821. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Amy DeCloux, Ph.D.
Patent Examiner,
May 3, 2001

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